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Letter

Palladium-Catalyzed [5 + 2] Rollover Annulation of 1-Benzylpyrazoles with Alkynes: A Direct Entry to Tricyclic 2-Benzazepines

Alejandro Suárez-Lustres, Nuria Martínez-Yáñez, Álvaro Velasco-Rubio, Jesús A. Varela, and Carlos Saá*

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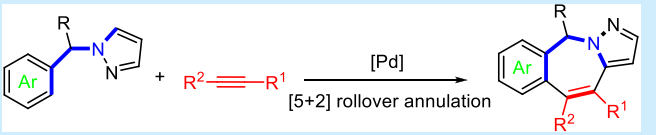
ABSTRACT: The first Pd-catalyzed [5 + 2] rollover annulation of 1-benzylpyrazoles with alkynes to assemble 10*H*-benzo[*e*]pyrazolo-[1,5-*a*]azepines (tricyclic 2-benzazepines) has been developed. The rollover annulation implies a twofold C−H activation of aryl and heteroaryl C_{sp^2}−H bonds (C−H/C−H) of 1-benzylpyrazoles (five-atom partners) and alkynes to give the [5 + 2] annulated compounds.



2-Benzazepines, in particular their hetero-fused tricyclic derivatives, are privileged structures present in a wide number of compounds with a diverse range of relevant biological activities, including Aurora kinase A,[1] bromodomain,[2] and acetylcholinesterase[3] inhibitory properties as well as anti-hepatitis C drugs[4] (Figure 1).

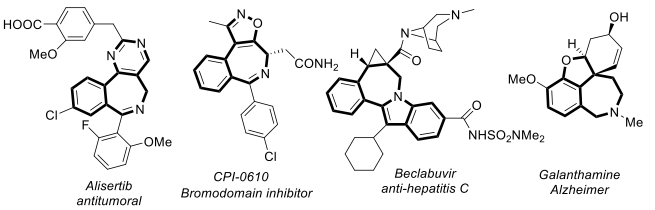
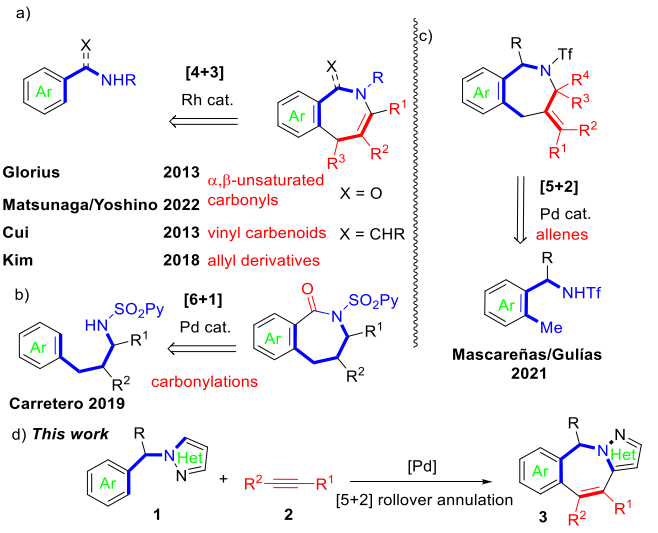


Figure 1. Biologically active tricyclic 2-benzazepines.

The remarkable biological activity of the 2-benzazepine scaffolds[5] and the synthetic appeal of assembling benzo-fused seven-membered N-heterocyclic rings has stimulated rich synthetic creativity throughout the years. These synthetic approaches range from classical condensations,[6] cyclizations,[7] and metal-catalyzed cycloadditions with imines[8] and nitriles[9] to the promising Pd-catalyzed intramolecular C−H hetero-arylations[10] and intermolecular carbopalladations[11] that allow rapid assembly of hetero-fused tricyclic derivatives. In recent years, more sustainable approaches based on intermolecular metal-catalyzed cycloadditions involving the direct activation of C−H bonds (oxidative annulations) have strongly emerged to build up medium-sized heterocycles.[12] Thus, for 2-benzazepin(on)es, Glorius, Matsunaga/Yoshino, and Cui independently developed a convergent Rh-catalyzed [4 + 3] cycloaddition between benzamides and α,β-unsaturated carbonyls[13] or vinylcarbenoids[14] (Scheme 1a). Besides, Kim developed a Rh-catalyzed [4 + 3] cycloaddition between *N*-allyl benzylamines and allyl derivatives (Scheme 1a).[15] On the other hand, Carretero exploited a Pd-catalyzed [6 + 1] cycloaddition of γ-arylpropylamine derivatives with CO (Scheme 1b).[16] These annulations involve initial C_{sp^2}−H activation followed by condensation or amidation reactions or, alternatively, CH/NH functionalizations. More recently,

Scheme 1. Metal-Catalyzed Oxidative Annulations to Form 2-Benzazepines



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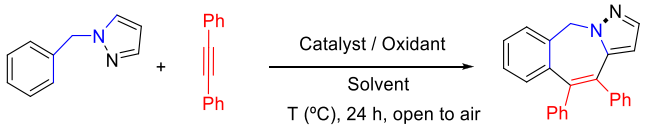
Mascareñas and Gulías described the first assembly of 2-benzazepines in an interesting formal [5 + 2] annulation process involving the activation of C_{sp^3}–H bonds (Scheme 1c).[17] Being aware of the capacity of pyrazoles to participate in metal-catalyzed C–H functionalizations[18] via rollover processes,[19] we herein report the first examples of efficient Pd-catalyzed [5 + 2] rollover annulations involving 1-benzylpyrazoles (five-atom partners) **1** with alkynes (two-carbon partners) **2** to afford tricyclic pyrazolo-2-benzazepines **3** in good to excellent yields (Scheme 1d). This rollover annulation implies an unusual twofold C–H activation of aryl and heteroaryl C_{sp^2}–H bonds (C–H/C–H), compared to the more typical annulation involving C–H/N–H activations (Scheme 1).

We started our investigation by testing the reactivity between 1-benzylpyrazole (**1a**) and diphenylacetylene (**2a**) as model partners under the known Miura's rollover conditions[18] for 1-phenylpyrazole (Table 1, entries 1–3).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

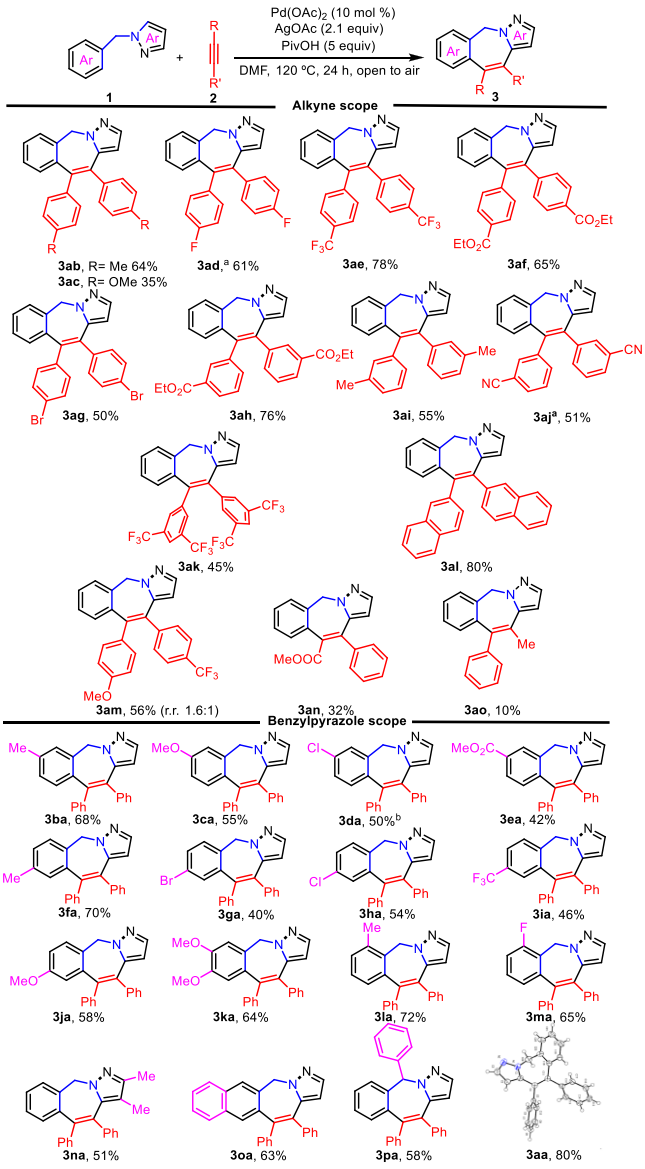
entry	cat.	oxidant	solvent[b]	T (°C)	yield (%)[c]
1[d]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2·H_2O$ Na_2CO_3	*m*-xyl	150	SM
2[d]	$[RhCp^*Cl_2]_2$	AgOAc	*m*-xyl	150	SM
3[d]	$[RhCp^*Cl_2]_2$	AgOAc	tol	100	SM
4	$Pd(OAc)_2$	$Cu(OAc)_2$	MeCN	105	20
5	$Pd(OAc)_2$	O_2/NaOAc	DMF	120	20
6	$Pd(OAc)_2$	BQ/AcOH	DMF	120	33
7	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	120	50
8	$Pd(OAc)_2$	AgOAc	DMF	120	64
9	$Pd(OAc)_2$	AgOAc + PivOH (1 equiv)	DMF	120	75
10	$Pd(OAc)_2$	AgOAc + PivOH (5 equiv)	DMF	120	88 (80)[e]
11[f]	$Pd(OAc)_2$	AgOAc + PivOH (5 equiv)	DMF	120	68

[a]Typical conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.3 mmol, 1.5 equiv), catalyst (10 mol %), oxidant (2.1 equiv), solvent (2.0 mL), air atmosphere, unless otherwise stated. [b]*m*-xyl, *m*-xylene; tol, toluene. [c]Determined by ^1H NMR analysis vs 1,3,5-trimethoxybenzene. The number in parentheses is the isolated yield. [d]$[RhCp^*Cl_2]_2$ (2.5 mol %). [e]At 90 °C, **3aa** was isolated in 73% yield. [f]**1a** (3 mmol), $Pd(OAc)_2$ (5 mol %).

Unfortunately, the reaction did not proceed with either $Cu(OAc)_2$ or AgOAc as the oxidant or xylene (150 °C) or toluene (100 °C) as the solvent. As the structure of **1a** contains a more flexible tetrahedral C_{sp^3} carbon compared to 1-phenylpyrazole, we thought that the formation of square-planar complexes might be more appropriate for catalytic C–H activation. Indeed, the reaction with $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant in MeCN gave the desired [5 + 2] rollover annulation product, tricyclic 2-benzazepine **3aa**,[19] although in a low 20% yield (Table 1, entry 4). Using O_2 as the oxidant or classical palladium/benzoquinone oxidative combinations in DMF gave slightly better yields of **3aa** (Table 1, entries 5 and 6). Typical metal oxidants like $Cu(OAc)_2$ and AgOAc in DMF gave moderate yields of **3aa** (Table 1, entries 7 and 8). Interestingly, using AgOAc and PivOH (1 equiv) as an additive, to favor a presumable CMD process,[20] led to **3aa** in a fairly good 75% yield (Table 1, entry 9).[21] To our delight, when the amount of PivOH was increased to 5 equiv, **3aa** was obtained in an excellent 80% isolated yield (Table 1, entry 10).[22] Under these conditions but using other solvents (e.g., toluene, DCE, MeCN, dioxane, *t*-AmOH, NMP, HFIP, etc.) at various temperatures gave poorer results.[23] To evaluate the practicality of this novel protocol, a scaled-up reaction was performed, leading to **3aa** in fairly good yield even with a reduced amount of catalyst (Table 1, entry 11). The structure of compound **3aa** was elucidated by X-ray diffraction analysis.

Having established the optimal conditions (Table 1, entry 10), we next investigated the scope and limitations of both reaction partners (Scheme 2). Symmetrical aryl alkynes **2b–2l**

Scheme 2. Scope of the Reaction[c]



[a]PivOH (10 equiv). [b]PivOH (15 equiv). [c]Reaction conditions: **1** (1 equiv), **2** (1.5 equiv), DMF (0.1 M), 120 °C, 24 h, open to air. The ORTEP drawing of **3aa** shows ellipsoids at the 30% contour probability level.

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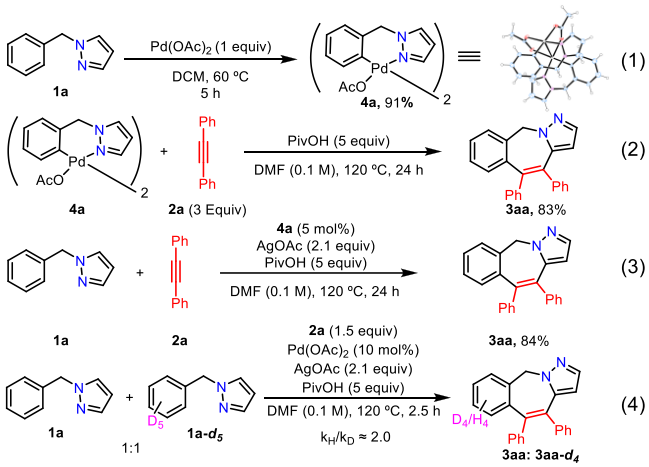
bearing an electron-donating group (Me, OMe) or an electron-withdrawing group (CF_3, F, COOMe) at the *para* or *meta* position were well-tolerated and gave the corresponding pyrazolo-2-benzazepines **3ab**−**3al** in moderate to good yields.[24] Pleasingly, aryl alkynes bearing halogens (Br, F) or coordinating groups (CN) afforded the products **3ad**, **3ag**, and **3aj** in relatively good yields. Unfortunately, dialkyl alkynes failed to react under the standard conditions.[25] On the other hand, the unsymmetrical diaryl alkyne **2m** bearing substituents with different electronic properties gave **3am** in 56% yield as a 1.6:1 mixture of regioisomers. Conjugated alkynes such as methyl 3-phenylpropiolate (**2n**) and 1-phenylpropyne (**2o**) regioselectively gave the corresponding pyrazolo-2-benzazepines **3an** and **3ao**, albeit in relatively low yields.

The electronic effects of aryl substituents in **1** were then analyzed. On the one hand, substrates with electron-withdrawing or electron-donating substituents at the *meta* or *para* position gave comparable results (**3ba**−**3ka**). Pleasingly, halogenated substituents were tolerated at both positions, which would enable their future functionalization (**3da, 3ga, 3ha**), as well as substitution in *ortho* position (**3la, 3ma**). On the other hand, substituents on the pyrazole ring were also allowed (**3na**). In addition, other substituted substrates such as naphthalenyl- and 1-benzhydrylpyrazoles also participated, giving the corresponding pyrazole-2-benzazepines **3oa** and **3pa** in fairly good yields.

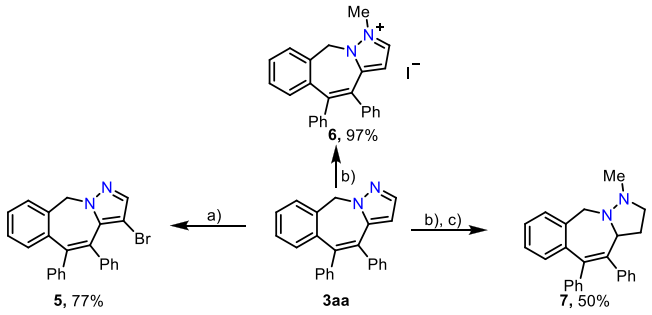
To gain insight into the reaction mechanism, a series of stoichiometric and catalytic experiments were conducted. The dimeric six-membered cyclometalated Pd(II) complex **4a**, which could be characterized by X-ray crystallography, was formed in 91% yield by heating **1a** with 1 equiv of $Pd(OAc)_2$ in DCM for 5 h (Scheme 3, eq 1).[26] Unlike the catalytic

Scheme 3. Mechanistic Studies



conditions (Table 1, entry 8), the stoichiometric reaction between dimeric palladacycle **4a** and alkyne **2a** needed the presence of PivOH to give **3aa** in 83% yield (Scheme 3, eq 2).[27] Pleasingly, palladacycle **4a** can act as a catalyst to give the target product **3aa** in 84% yield under the optimized conditions (Scheme 3, eq 3). The competition between **1a** and the deuterated analogue **1a-*d*$_5$** showed a nonconclusive primary kinetic isotopic effect, suggesting that the first C−H bond activation might be the rate-determining step (Scheme 4, eq 4).

Scheme 4. Derivatizations of 3aa



With all these experimental data on hand, density functional theory (DFT) calculations[23] for the reaction of **1a** with **2a** catalyzed by $^1/_2Pd_2(OAc)_4$ in the presence of $^1/_2(AgOAc)_2$ and AcOH in DMF were performed. According to Fang and co-workers,[28] starting materials coordinated to mononuclear palladium species represent the most plausible structures of the initial reaction complex under catalytic conditions. We started our calculations from complex **I**, which is isoenergetic with the starting materials (Figure 2).[29] After agostic interaction of the *ortho* hydrogen of the phenyl ring in intermediate **II**,[29] C−H activation would take place through $\mathbf{TS_{II-III}}$ (16.8 kcal mol^{-1}) to give the six-membered palladacycle **III** lying at −7.4 kcal mol^{-1}.[30] Then 1,2-migratory insertion of the alkyne into the C−Pd bond occurs, most probably from Pd^{II}−Ag^{I} bimetallic species **IV** through $\mathbf{TS_{IV-V}}$ at 12.2 kcal mol^{-1}, after which N-decoordination gives **V**.[31] Further decoordination of AgOAc to give **VI**[31] followed by a CMD process through $\mathbf{TS_{VI-VII}}$ (8.8 kcal mol^{-1}) affords palladacycle **VII** (rollover process). Recoordination of AgOAc to form **VIII** followed by reductive elimination through $\mathbf{TS_{VIII-IX}}$ (7.5 kcal mol^{-1}) would release **3aa** from the Pd^0−Ag^I bimetallic complex **IX** ($\Delta G°$ = −17.7 kcal mol^{-1}).[31] An alternative mechanism involving a Pd(IV) species to favor a reductive elimination step was discarded since a catalytic reaction in the presence of oxidants ($PhI(OAc)_2$, PIFA, Oxone, NFSI) failed while a stoichiometric experiment with $Pd^{II}(OAc)_2$ and PivOH in the absence of AgOAc gave **3aa** in almost quantitative yield.[23]

However, under stoichiometric conditions, formation of the binuclear Pd species **4a** would be more plausible,[28] which cannot undergo the 1,2-migratory insertion of the alkyne due to the high activation energy barrier ($\Delta G^{‡}$ = 35.8 kcal mol^{-1}) as experimentally observed.[23] By using large amounts of an external ligand (PivOH or **1a**; Scheme 3, eqs 2 and 3),[23] the reaction would return to the mononuclear Pd catalytic cycle, which is able to afford the product **3aa**.

Derivatizations of benzo[*e*]pyrazolo[1,5-*a*]azepine **3aa** were then analyzed (Scheme 4). Electrophilic bromination with NBS at room temperature afforded 4-bromopyrazole derivative **5** in a fairly good yield (77%, a). Alkylation with methyl iodide gave rise to pyrazolium salt **6** in an excellent 97% yield (b). Interestingly, reduction of the pyrazole to the tetrahydro derivative **7** could be accomplished using $NaBH_4$ in EtOH at 60 °C in 50% yield (c).[32]

In summary, we have developed a new Pd-catalyzed rollover annulation of 1-benzylpyrazoles with alkynes to obtain benzo[*e*]pyrazolo[1,5-*a*]azepines (tricyclic 2-benzazepines). The seven-membered azepine ring was built based upon a new [5 + 2] rollover annulation that implies a twofold C−H activation of aryl and heteroaryl C_{sp^2}−H bonds (C−H/C−H) of 1-benzylpyrazoles with alkynes. The pyrazole moiety of the

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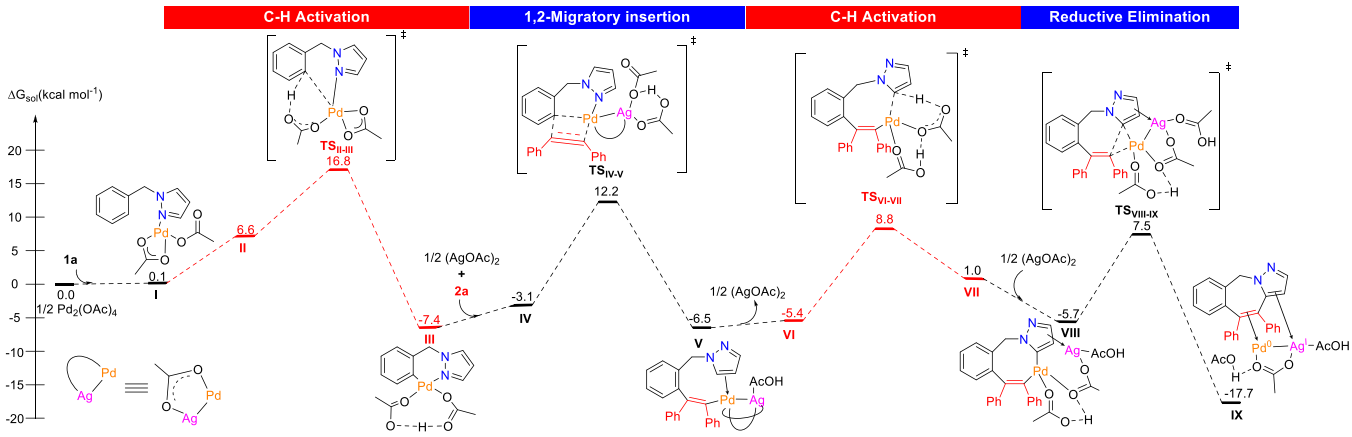

Figure 2. Free energy profile for the [5 + 2] rollover annulation of 1-benzylpyrazole (**1a**) with 1,2-diphenylacetylene (**2a**) catalyzed by monometallic Pd^{II} (in red) and bimetallic Pd^{II}–Ag^{I} (in black) species. Computational studies were performed at the B3LYP-D3/6-311++G(d,p)-cc-pVTZ-pp$_{DMF(SMD)}$//B3LYP-D3/6-31G(d,p)-LANL2DZ$_{DMF(SMD)}$ level. Energies are relative to $^{1}/_{2}Pd_2(OAc)_4$ combined with those of the relevant substrates.

tricyclic 2-benzazepines can be readily functionalized, which highlights the potential utility of our approach. Further applications are currently in progress in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c04300.

General experimental procedures, X-ray crystallographic data, and NMR spectra (PDF)

Accession Codes

CCDC 2208317 (**3aa**) and 2208318 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Carlos Saá − *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain;* orcid.org/0000-0003-3213-4604; Email: carlos.saa@usc.es

Authors

Alejandro Suárez-Lustres − *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*

Nuria Martínez-Yáñez − *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*

Álvaro Velasco-Rubio − *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*

Jesús A. Varela − *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain;* orcid.org/0000-0001-8499-4257

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c04300

Notes

The authors declare no competing financial interest.

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